

WO9962872

Publication Title:

3-aryl-2-hydroxypropionic acid derivative (I)

Abstract:

A novel 3-aryl-2-hydroxypropionic acid derivative, a process and intermediate for its manufacture, pharmaceutical preparations containing it and the use of the compound in clinical conditions associated with insulin resistance.

Data supplied from the esp@cenet database - <http://ep.espacenet.com>

BEST AVAILABLE COPY

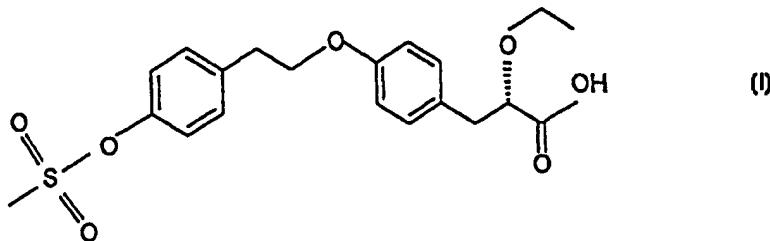


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 309/66, A61K 31/19	A1	(11) International Publication Number: WO 99/62872 (43) International Publication Date: 9 December 1999 (09.12.99)
---	----	---

(21) International Application Number: PCT/SE99/00941 (22) International Filing Date: 31 May 1999 (31.05.99) (30) Priority Data: 9801992-0 4 June 1998 (04.06.98) SE (71) Applicant (<i>for all designated States except US</i>): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (<i>for US only</i>): ANDERSSON, Kjell [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
	Published <i>With international search report.</i>

(54) Title: NEW 3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVE (I)



(57) Abstract

A novel 3-aryl-2-hydroxypropionic acid derivative, having formula (I) and pharmaceutically acceptable salts, solvates, and crystalline forms thereof, a process and intermediate for its manufacture, pharmaceutical preparations containing it and the use of the compound in clinical conditions associated with insulin resistance.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

NEW 3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVE I

Field of invention

5

The present invention relates to a novel 3-aryl-2-hydroxypropionic acid derivative, to a process and intermediate for preparing such a compound, having the utility in clinical conditions associated with insulin resistance, to methods for its therapeutic use and to pharmaceutical compositions containing it.

10

Background of the invention

Insulin resistance, defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, fat and liver prevail in many 15 individuals with or without diabetes mellitus. The insulin resistance syndrome, IRS, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly non insulin dependent diabetes mellitus (NIDDM); arterial hypertension; central (visceral) obesity; dyslipidemia observed as deranged lipoprotein levels typically characterized by elevated VLDL (very low density lipoproteins) and 20 reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In non-insulin dependent diabetes mellitus these 25 atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is at present only limited awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis.

Furthermore there is at present no pharmacotherapy available to adequately correct the metabolic derangements associated with IRS. To date, the treatment of NIDDM has been focused on correction of the deranged control of carbohydrate metabolism associated with the disease. Stimulation of endogenous insulin secretion by means of secretagogues, like sulphonylureas, and if necessary administration of exogenous insulin are methods frequently used to normalize blood sugar but that will, if anything, further enhance insulin resistance and will not correct the other manifestations of IRS nor reduce cardiovascular morbidity and mortality. In addition such treatment involves a significant risk of hypoglycemia with associated complications.

10

Other therapeutic strategies have focused on aberrations in glucose metabolism or absorption, including biguanides, such as metformin, or glucosidase inhibitors, such as acarbose. Although these agents have been efficacious to a degree, their limited clinical effect is associated with side effects.

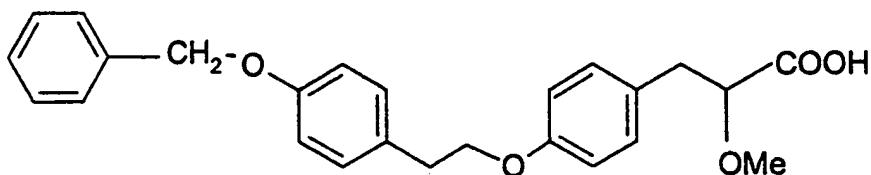
15

A novel therapeutic strategy involves the use of insulin sensitizing agents, such as the thiazolidinediones, which, at least in part, mediate their effects via an agonistic action on nuclear receptors. Ciglitazone is the prototype in this class. In animal models of IRS these compounds seem to correct insulin resistance and the associated hypertriglyceridaemia and 20 hyperinsulinemia, as well as hyperglycemia in diabetes, by improving insulin sensitivity via an effect on lipid transport and handling, leading to enhanced insulin action in skeletal muscle, liver and adipose tissue.

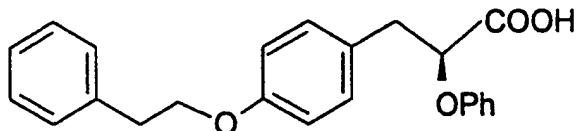
Ciglitazone as well as later described thiazolidinediones in clinical development either 25 have been discontinued reportedly due to unacceptable toxicity or show inadequate potency. Therefore there is a need for new and better compounds with insulin sensitizing properties.

Prior art

Compounds of the formula



and



and certain derivatives thereof disclosed in US 5 306 726 and WO 91/19702 are said to be useful as hypoglycemic and hypocholesterolemic agents, and in US 5 232 945 said to be useful in the treatment of hypertension.

15 AU 650 429 discloses structurally related compounds, but claimed to have different properties: diuretic, antihypertensive, platelets anti-aggregating and anti-lipoxygenase properties.

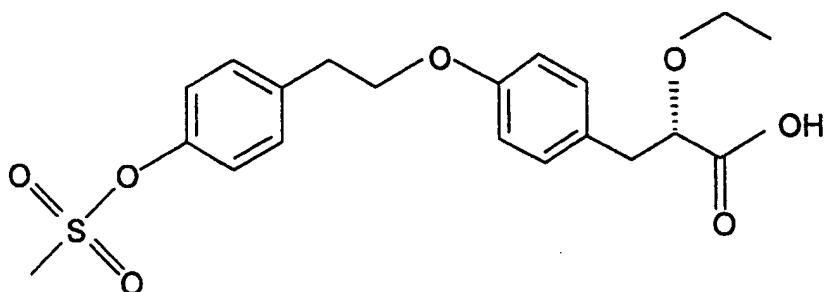
20 EP 139 421 discloses compounds having the ability to lower blood lipid and blood sugar levels. Among these compounds is troglitazone, a compound that has reached the market for treatment of NIDDM or decreased glucose tolerance.

Description of the invention

It has now surprisingly been found that the novel compound

(S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

5 having the formula I



is effective in conditions associated with insulin resistance.

10

The invention also relates to pharmaceutically acceptable salts, solvates, such as hydrates, and crystalline forms of the compound of the formula I.

15

In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to such salts as the alkali metal salts (e.g. sodium, lithium and potassium), alkaline earth metal salts (e.g. calcium, barium and magnesium), aluminium, zinc and bismuth salts, ammonium salts, salts with basic amino acids, such as arginine, lysine, and salts with organic amines such as ethanolamine, ethylenediamine, triethanolamine, benzylphenethylamine, diethylamine, tromethamine, benzathine, chloroprocaine, choline, meglumine, procaine, clemizole and piperazine.

20

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all pharmaceutically acceptable salts thereof, crystalline forms and solvates thereof such as for instance hydrates.

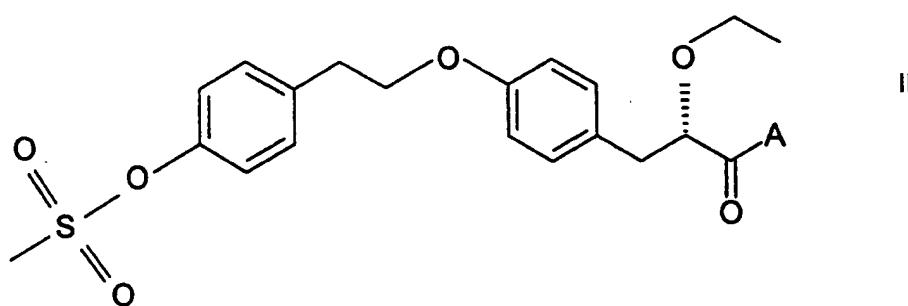
25

Methods of preparation

5 The compound of the invention may be prepared as outlined below according to any of methods A-H. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

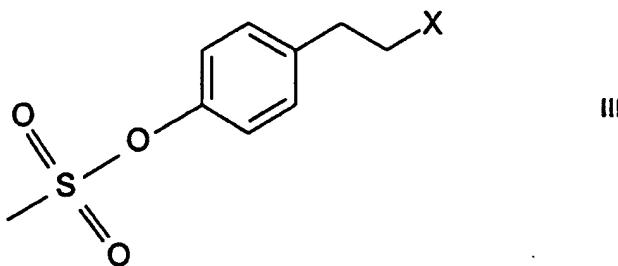
A. The compound of the invention of the formula I, can be prepared by converting a compound of formula II

10



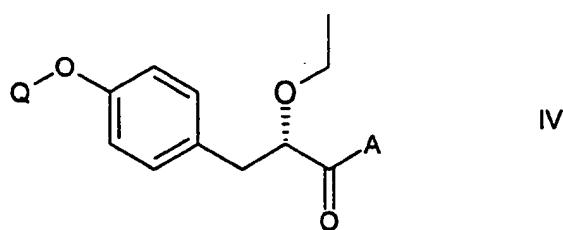
15 wherein A is -OR^P, wherein R^P is a protective group, e.g. ethyl, or A is a chiral auxiliary group, such as a chiral amine, e.g. (R)-fenylglycinol, a chiral alcohol, such as menthol or a chiral oxazolidinone, such as (S)-4-benzyl-2-oxazolidinone. The conversion can be performed as a hydrolysis which can be either acidic or basic and performed according to standard methods known to anyone skilled in the art or as described in the experimental part.

20 B. The compound of the formula I or the formula II, wherein A is a chiral auxiliary group or -OR^P and R^P is as defined above, can be prepared by reacting a compound of the formula III



wherein X is OH or a leaving group such as a sulfonate or a halogen, with a compound of the formula IV

5



wherein Q is H and A is a chiral auxiliary group, -OH or -OR^P, and R^P is as defined above. The reaction can be performed either by an alkylation reaction or a Mitsunobu reaction.

10

In an alkylation reaction the leaving group X can be a sulfonate such as mesylate, nosylate, tosylate, or a halogen, such as bromine or iodine. The compounds of formula III and IV, in approximately equimolar amounts or with an excess of either compound, are heated to reflux temperature in an inert solvent, such as isopropanol or acetonitrile, in the presence of a base, such as potassium carbonate or cesium carbonate.

15

The mixture is refluxed for the necessary time, typically between 0.5 h to 24 h, the work up procedure usually includes filtration, for removal of solid salt, evaporation, neutralisation (when A=OH) and extraction with water and an organic solvent such as dichloromethane, ethyl acetate, or diethyl ether.

20

The crude product is purified if desired e.g. by recrystallization or by standard chromatographic methods.

The Mitsunobu reaction can be carried out according to standard methods or as described in for example Tsunoda T., Yamamiya Y., Ito S., Tetrahedron Letters, 34, 1639-1642 (1993) or O. Mitsunobu, Synthesis, 1981, p.1. When using a Mitsunobu reaction A can not be -OH.

5

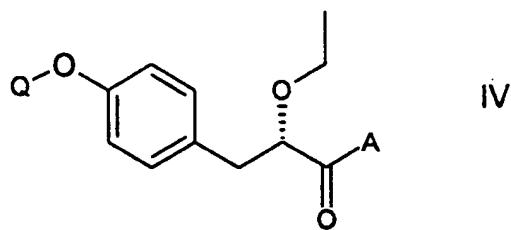
In a typical Mitsunobu reaction a compound of formula III, wherein the group X is a hydroxyl group, and a compound of formula IV are mixed, in approximately equimolar amounts or with an excess of either compound, in an inert solvent, such as chloroform, dichloromethane, or tetrahydrofuran. A slight molar excess, 1-4 equivalents, of an azodicarboxylate, such as DEAD or ADDP and a phosphine (1-4 equivalents), such as tributylphosphine or triphenylphosphine are added and the reaction is stirred at a temperature high enough - for example room temperature - and a time long enough (1-24 hours) to obtain product, which can be worked up with standard literature methods and if desired purified, e.g. by standard chromatographic methods.

15

The compound of formula III can be prepared by standard procedures known to anyone skilled in the art, from commercially available starting materials or as described in the experimental section.

20

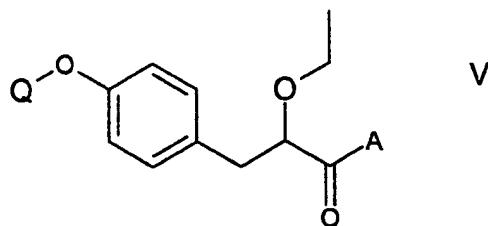
The compound of formula IV wherein Q is H and A is a chiral auxiliary group, -OH or -OR^P, wherein R^P is as defined above, can be prepared as described below in the experimental part or by converting a compound of formula IV



25

wherein Q is R^q, wherein R^q is a protective group, e.g. benzyl, and A is a chiral auxiliary group, -OH or -OR^P wherein R^P is as defined above.

C. The compound of formula II, wherein A is a chiral auxiliary group, and the compound of formula IV, wherein A is a chiral auxiliary group and Q is hydrogen or R^q, wherein R^q is as defined above and, can be prepared by diastereoisomeric separation of the compound of the formula V

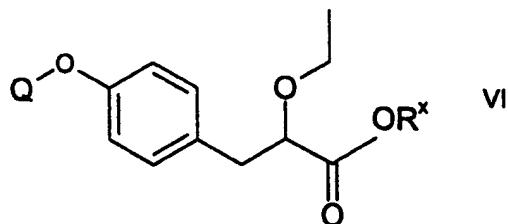


10

wherein A is a chiral auxiliary group, Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above. The separation of the diastereomers can be performed either by crystallization or by chromatography. The chromatographic separation can be performed as described in the experimental part.

15

The compound of formula V wherein A is a chiral auxiliary group, Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, can be prepared by converting a compound of formula VI



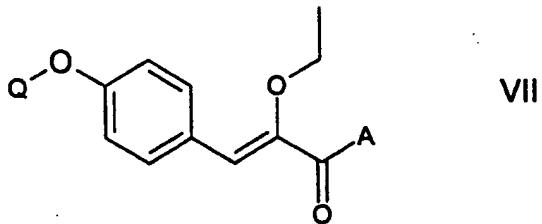
20

wherein Q is hydrogen, $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$, or R^q , and R^x is hydrogen or R^p , wherein R^q and R^p are as defined above, for example by reacting it with a chiral amine or a chiral alcohol.

- 5 The compound of formula V when A is a chiral amine can be prepared by reacting a compound of formula VI with a chiral amine such as (R)-phenyl glycinol for example in the presence of a peptide coupling system (e.g. EDC, DCC, HBTU, TBTU, PyBop or oxalylchloride in DMF), an appropriate base (e.g. pyridine, DMAP, TEA or DiPEA) and a suitable organic solvent (e.g. dichloromethane, acetonitrile or DMF) in accordance to methods well known to those skilled in the art or as described in the examples.
- 10 methods well known to those skilled in the art or as described in the examples.

The compound of formula V when A is a chiral alcohol can be prepared in the same way using a chiral alcohol, such as menthol, instead of a chiral amine, or by the mix-anhydride method with pivaloyl chloride and the lithium salt of the chiral alcohol.

- 15 The compound of formula V wherein A is a chiral auxiliary group and Q is hydrogen, $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$, or R^q , wherein R^q is as defined above, and the compound of formula VI, wherein Q is hydrogen, $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$, or R^q and R^x is hydrogen or R^p , wherein R^q and R^p are as defined above, can be prepared by reduction of a compound
- 20 of formula VII



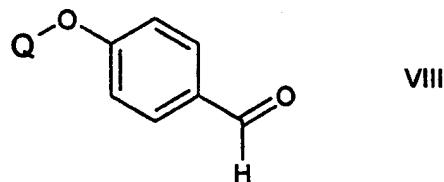
- 25 wherein A is a chiral auxiliary group, -OH, or -OR^p wherein R^p is as defined above and Q is hydrogen, $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$, or R^q , wherein R^q is as defined above, and if desired followed by removal of protecting groups.

The reduction of the olefin may be carried out by using a wide variety of reducing methods known to reduce carbon-carbon double bonds, such as catalytic hydrogenation in 5 the presence of an appropriate catalyst or hydrogen transfer reagents such as diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

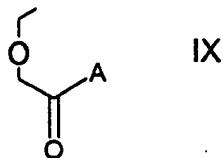
The catalytic hydrogenation can be performed in alcohol, cellosolves, protic polar organic solvents, ethers, lower alifatic acids, and particularly in methanol, ethanol, 10 methoxyethanol, dimethylformamide, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate or acetic acid either used alone or in mixture. Examples of the catalysts used include palladium black, palladium on charcoal, platinum oxide or Wilkinson's catalyst. This reaction can be performed at different temperatures and pressures depending on the reactivity of the aimed reaction.

15 In case of hydrogen transfer reaction with diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate the reaction can be conducted by mixing equimolar amounts of reactants and warming the mixture to melting (140-250°C) in inert atmosphere or in vacuum.

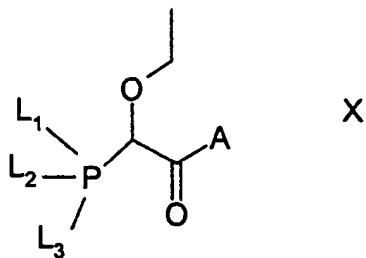
- 20 The compound of formula VII wherein A is a chiral auxiliary group, -OH, or -OR^p, wherein R^p is as defined above and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, can be prepared by a condensation reaction, such as a Knoevenagel or Wittig type reaction, of a carbonyl compound of the formula VIII



wherein Q is hydrogen, $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$ or R^q , wherein R^q is as defined above, with a compound of the formula IX



- 5 in which formula A is a chiral auxiliary group, $-\text{OH}$ or $-\text{OR}^p$, wherein R^p is as defined above, or a compound of the formula X



- 10 in which formula A is a chiral auxiliary group or $-\text{OR}^p$, wherein R^p is as defined above, $\text{L}^1 = \text{L}^2 = \text{L}^3$ are phenyl or $\text{L}^1 = \text{L}^2$ are $-\text{Oalkyl}$ and L^3 is $= \text{O}$, and, if desired, followed by removal of protecting groups or by an arylation reaction as described in for example Cacchi S., Ciattini P. G., Morera E., Ortari G., Tetrahedron Letters, 28 (28) 1987, pp 3039-3042.

15

In the condensation step, approximately equimolar amounts of reactants are mixed in the presence of a base, to provide the olefin compound. This step may be carried out in the presence of an inert solvent or in the absence of a solvent at a temperature between -20°C and the melting point for the mixture. It might be necessary to add a dehydrating agent in order to achieve the olefinic compound.

In a typical such reaction the compounds of formula VIII and formula IX are mixed in a solvent such as tetrahydrofuran. Anhydrous potassium *tert*-butoxide is slowly added at low temperature i.e. -20°C . The reaction is quenched with acetic acid. The crude product is

isolated, redissolved in toluene and refluxed with p-toluene sulfonic acid in a Dean-Stark apparatus. The solution is cooled and the product is isolated and purified according to standard methods (see Groger T., Waldmann E., Monatsh Chem 89, 1958, p 370).

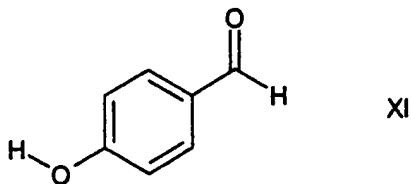
- 5 The condensation step could also be performed as a Wittig-type reaction (see for example Comprehensive Organic Synthesis vol. 1 p. 755-781 Pergamon Press) or as described in the experimental part.

In a typical such reaction, approximately equimolar amounts of reactants of formula VIII and formula X are stirred in the presence of a base such as tetramethylguanidine or

- 10 potassium carbonate in a 1-5 fold molar excess. This step may be carried out in the presence of an inert solvent such as dichloromethane or acetonitrile and at a suitable temperature (-10° C + 60° C) and at a time long enough.

The compound of the formula VIII when Q is -CH₂CH₂Ph-4-OSO₂CH₃ can be prepared by

- 15 coupling a compound of the formula III wherein X is -OH or a leaving group such as a sulfonate or a halogen, with a compound of the formula XI

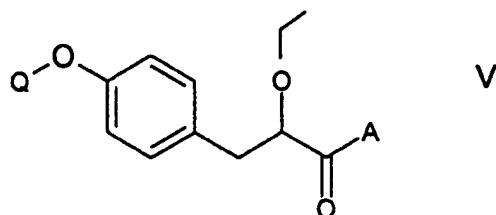


20

When X is a leaving group such as a sulfonate or a halogen, the reaction may be performed as an alkylation reaction and when X is -OH, as a Mitsunobu reaction as described above.

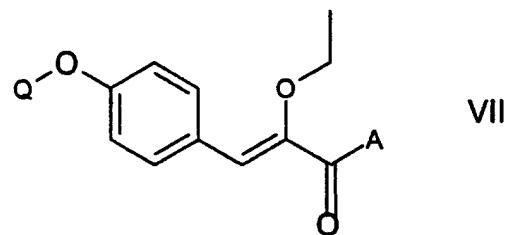
- 25 D. The compound of formula I or formula II wherein A is -OR^P and R^P is as defined above and the compound of formula IV wherein A is OH or -OR^P and Q is H or R^Q wherein R^P

and R^q are as defined above can be prepared by enantiomeric separation, such as chiral chromatography of the compound of the formula V



- 5 wherein A is -OH or -OR^P, Q is H, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q wherein R^P and R^q are as defined above.

E. The compound of the formula I or the formula II wherein A is a chiral auxiliary group or -OR^P, wherein R^P is as defined above, and the compound of formula IV wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen or R^q, wherein R^q is as defined above and, can be prepared by asymmetric reduction of a compound of the formula VII



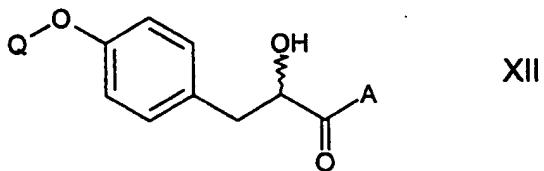
15

wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃, or R^q, wherein R^q is as defined above.

The asymmetric reduction can be carried out using a wide variety of reducing methods known to reduce carbon-carbon double bonds such as catalytic hydrogenation in the presence of an appropriate chiral catalyst such as Rh-BINAP or [Et-DuPHOS-Rh(COD)] or catalytic hydrogenation with an appropriate catalyst, such as palladium on charcoal using the chiral auxiliary group to induce the asymmetry.

The catalytic hydrogenation can be carried out in a wide variety of solvents, such as alcohol, cellosolves, protic polar organic solvents, ethers, lower alifatic acids, and particularly in methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate or acetic acid, either used alone or in a mixture. The reaction can proceed at different temperatures and pressures depending on the reactivity of the aimed reaction.

F. The compound of the formula I or the formula II, wherein A is a chiral auxiliary group, or -OR^P, wherein R^P is as defined above, and the compound of formula IV wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen or R^Q, wherein R^Q is as defined above, can be prepared by alkylating a compound of the formula XII



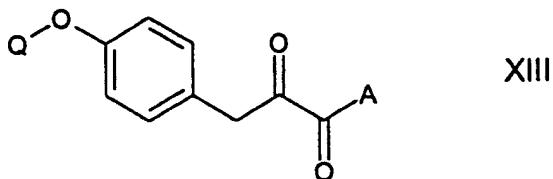
15

wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃, or R^Q, wherein R^Q is as defined above, with the required stereochemistry dependent on the reaction conditions used.

20 The alkylation may be carried out using a variety of alkylating agents, such as ethyl halide or diethyl sulfate (see for example Benedict D.R., Bianchi T.A., Cate L.A., Synthesis (1979), pp. 428-429, Barluenga J., Alonso-Cires L., Campos P.J., Asensio G., Synthesis, 1983, p. 53-55, Bull Chem Soc Jpn, 1986, 59, 2481, S. Patai, The Chemistry of the Ether Linkage, Wiley-Interscience NY, 1967, 445-498 or Survey of Organic Synthesis vol 1, Wiley-Interscience 1970, NY, p. 285-328).

The compound of formula XII wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, can be prepared by asymmetric reduction of a compound of the formula XIII

5



wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above.

10

The asymmetric reduction may be performed by using a wide variety of reducing methods which are known to reduce ketones enantioselectively (see Flynn G.A., Beight D.W., Tetrahedron Letters, 29(4), 1988, pp. 423-426).

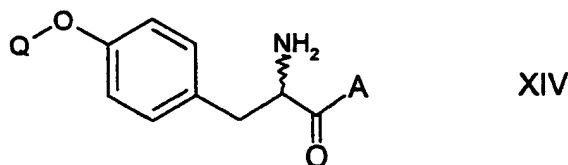
15

The compound of formula XII wherein A is a chiral auxiliary group and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, may also be prepared by induced chiral reduction of a compound of formula XIII, wherein A is a chiral auxiliary group and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above (see Xiang Y.B., Snow K., Belley M., J. Org. Chem., 1993, 58, pp 993-994).

20

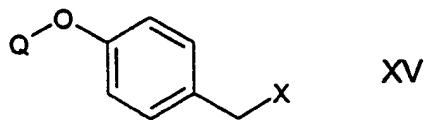
The compound of formula XII, wherein A is a chiral auxiliary group, -OH or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, can be prepared by converting a compound of the formula XIV

25

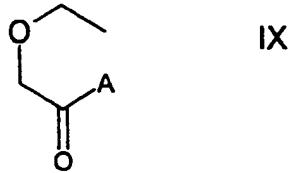


wherein A is a chiral auxiliary group, -OH or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH₂CH₂Ph-4-OSO₂CH₃ or R^Q, wherein R^Q is as defined above, with the required stereochemistry, dependent on the reaction conditions used (see for example K. Koga, C.C. Wu and S. Yamada, Tetrahedron Letters, no. 25, 1971, p 2283-2286 , Kunz H., Lerchen H-G., Tetrahedron Letters, 28 (17) 1987, pp.1873-1876).

G. The compound of formula II, wherein A is a chiral auxiliary group, and the compound of formula IV wherein A is a chiral auxiliary group and Q is R^Q, wherein R^Q is as defined above, can be prepared by reacting a compound of formula XV



wherein X is a leaving group, such as a halogen or a sulfonate, and Q is -CH₂CH₂Ph-4-OSO₂CH₃ or R^Q, wherein R^Q is as defined above, with a compound of the formula IX



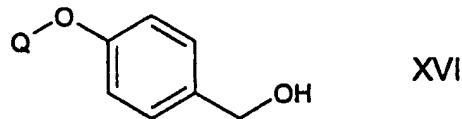
wherein A is a chiral auxiliary group.

20

In the alkylation step the compound of formula XV is reacted with a compound of formula IX in the presence of one or more bases such as potassium carbonate, triethylbenzyl-ammonium chloride, sodium hydride, LDA, butyllithium or LHMDS in an inert solvent such as acetonitrile, DMF or dichloromethane at a suitable temperature and time. The

reaction can be carried out using standard methods known in the litterature. (see for example Pearsson W.H., Cheng M.C., J. Org. Chem., 51 (19) 1986, 3746-3748, Myers A.G., Yang B.H., Gleason J.L., J. Am. Chem. Soc. 1994, 116, pp 9361-9362, Negrete G.R., Konopelski J.P., Tetrahedron Assymetry, 2, 2, pp. 105-108, 1991, Davies S.G., 5 Sanganee H.J., Tetrahedron Assymetry, 6, 3, pp. 671-674, 1995, Hulin B., Newton L.S., Lewis D.M., Genereux P.E., Gibbs E.M., Clark D.A. J. Med.Chem. 39, 3897-3907 (1996) and Savignac M., Durand J-O, Genet J-P, Tetrahedron Assymetry, 5, 4, pp.717-722, 1994).

10 The compound of formula XV wherein X is a leaving group, such as a halogen or a sulfonate, and Q is -CH₂CH₂Ph-4-OSO₂CH₃, or R^q, wherein R^q is as defined above, can be prepared from a compound of formula XVI



15 wherein Q is -CH₂CH₂Ph-4-OSO₂CH₃, or R^q, wherein R^q is as defined above, using standard methods known to anyone skilled in the art.

The compound of formula XVI wherein Q is - CH₂CH₂Ph-4-OSO₂CH₃ or R^q, wherein R^q is as defined above, can be prepared by reduction of a compound of formula VIII, wherein 20 Q is -CH₂CH₂Ph-4-OSO₂CH₃, or R^q, wherein R^q is as defined above, by standard methods known to anyone skilled in the art.

H. The compound of the invention of formula I and the compound of formula IV, wherein A is -OH and Q is hydrogen or R^q, wherein R^q is as defined above, can be prepared by 25 resolution of the racemate thereof and, if desired, followed by neutralization.

The resolution can be performed by separative crystallization of a salt consisting of the racemate of, either the compound of the invention of formula I, or the compound of formula IV, and a chiral base, such as quinine, in an inert solvent such as ethyl acetate or

toluene (see for example Duhamel P., Duhamel L., Danvy D., Plaquevent J. C., Giros B., Gros C., Schwartz J.C., Lecomte J.M., US 5136076, Stephani R., Cesare V., J. Chem. Ed., 10, 1997, p. 1226 and Yamamoto M., Hayashi M., Masaki M., Nohira H., Tetrahedron Assymetry, 2, 6, pp. 403-406, 1991).

5

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain the compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

15

In any of the preceding methods of preparation A-H, where necessary, hydroxy, amino or other reactive groups may be protected using a protecting group, R^P or R^Q as described in the standard text "Protective groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protecting group R^P or R^Q may also be a resin, such as Wang resin or 2-chlorotriyl chloride resin. The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art.

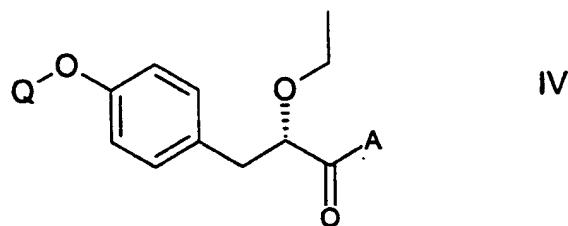
25 The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Unless otherwise stated or indicated the term chiral auxiliary group denotes a chiral group, 30 such as a chiral alcohol or amine, for instance (-)-menthol, (+)-isomenthol, (-)-norneol,

(R)-2-phenyl glycinol, (S)-2-phenyl glycinol, (R)-4-phenyl-2-oxazolidinone or (S)-4-benzyl-2-oxazolidinone, which when connected to a carbonyl group easily can be cleaved to the corresponding acid.

5 Intermediates

When preparing the compound of formula I of the invention an intermediate of the formula IV



10

wherein Q is hydrogen and A is -OH or -OR^P, wherein R^P is a protective group, e.g. ethyl, or A is a chiral auxiliary group, such as a chiral amine, e.g. (R)-fenylglycinol, or a chiral alcohol, such as menthol or a chiral oxazolidinone, such as (S)-4-benzyl-2-oxazolidineone, 15 is particularly useful. It is prepared as described above. Under the same heading its use as intermediate for the preparation of the end compound of the invention is described.

Pharmaceutical preparations

The compound of the invention will normally be administered via the oral, parenteral, intravenous, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in
5 the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

10

The compound of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidemias, dyslipidemias, diabetes and obesity.

15 Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.005-5 mg/kg body weight, preferably 0.01-0.5 mg/kg body weight.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention, or pharmaceutically acceptable
20 derivatives thereof, in optional admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

25 The present compound of formula (I) will be adapted for prophylaxis and/or treatment of clinical conditions associated with reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders. These clinical conditions will include, but will not be limited to, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia (non insulin dependent diabetes mellitus (NIDDM)) and the dyslipidaemia (plasma
30 lipoprotein disturbances) characteristically appearing with insulin resistance. This

dyslipidaemia, also known as the atherogenic lipoprotein profile of phenotype B, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoproteins (VLDL) triglycerides, low high density lipoproteins (HDL) cholesterol and the presence of small, dense, low density lipoproteins (LDL). Treatment with the present compound is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis. These cardiovascular disease conditions include macro-angiopathies causing myocardial infarction, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compound of formula (I) is also expected to reduce the progress of clinical conditions associated with chronic hyperglycaemia in diabetes like the micro-angiopathies causing renal disease and retinal damage. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system associated with insulin resistance like the polycystic ovarian syndrome. The compound of the invention is a non-toxic insulin sensitizing agent with surprisingly good therapeutic effect and pharmacokinetic properties and without undesirable weight gain.

General Experimental Procedures

¹H NMR and ¹³C NMR measurements were performed on a BRUKER ACP 300 and Varian UNITY plus 400 and 500 spectrometers, operating at ¹H frequencies of 300, 400 and 500 MHz respectively, and at ¹³C frequencies of 75, 100 and 125 MHz respectively.

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

25

Working examples

Example 1.

(S)-2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

30

a) 2-(4-Methanesulfonyloxyphenyl)ethylmethanesulfonate

p-Hydroxyphenethylalcohol (15 g; 0.108 mole) was dissolved in dichloromethane. Triethylamine (27.3 g; 0.27 mole) was added followed by addition of a solution of methanesulfonyl chloride (27.2 g; 0.239 mole) in dichloromethane at 0° C. The reaction mixture was allowed to reach room temperature, then stirred at room temperature and followed by TLC. The reaction mixture was filtered and the filtrate was washed with water. The organic phase was dried with sodium sulfate and then evaporated *in vacuo* to give 28 g (yield 88%) of 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate.

10

¹H-NMR (400 MHz; CDCl₃): δ 2.85 (s, 3H), 3.05 (t, 2H), 3.15 (s, 3H), 4.35 (s, 2H), 7.2 (dm, 2H), 7.25 (dm, 2H).

¹³C-NMR (100 MHz; CDCl₃): δ 34.8, 37, 27, 37, 31, 69.6, 122.2, 130.5, 135.8, 148.1.

15

b) 4-[2-(4-Formylphenoxy)ethyl]phenylmethanesulfonate

2-(4-Methanesulfonyloxyphenyl)ethylmethanesulfonate (30 g; 0.102 mole) was dissolved in acetonitrile and slowly added to a mixture of p-hydroxybenzaldehyde (31.1 g; 0.255 mole) and potassium carbonate (41.46 g; 0.3 mole) in acetonitrile. The resulting mixture was refluxed until 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate was consumed. The salts were filtered off, the solvent evaporated *in vacuo*, dichloromethane was added and the organic phase was washed with water. After evaporation of the solvent, purification by chromatography on silica gel using dichloromethane as eluant gave 21.6 g (yield 66 %) of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate.

¹H-NMR (400 MHz; CDCl₃): δ 3.05-3.15 (t, 2H+s, 3H), 4.2 (t, 2H), 6.95 (dm, 2H), 7.2 (dm, 2H), 7.3 (dm, 2H), 7.8 (dm, 2H), 9.8 (s, 1H).

¹³C-NMR (100 MHz; CDCl₃): δ 37.3, 38.3, 63.4, 116.1, 122.1, 129.2, 130.6, 132.6, 138.1, 147.7, 162.6, 191.7.

c) 2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

5

Tetramethylguanidine (9 g; 78 mmole) was slowly added to a solution of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate (27 g; 84.2 mmole) and (1,2-diethoxy-2-oxyethyl)triphenylphosphonium chloride (30 g; 72 mmole) in chloroform (300 ml) at 0°C. After stirring at room temperature over night the solvent was evaporated *in vacuo*. Diethyl ether was added to the residue and insoluble material was filtered off. More diethyl ether was added and the mixture was filtered again. The filtrate was washed with sodium hydrogen carbonate solution. The organic phase was dried (magnesium sulfate) and the solvent was evaporated. Recrystallization of the residue in ethanol gave 20.2 g (yield 64.6 %) of 2-ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)-ethoxy]phenyl}acrylic acid ethyl ester.

10
15
20
¹H-NMR (500 MHz; CDCl₃): δ 1.34-1.38 (2t, 2x6H, J=7 Hz for both), 3.11 (t, 2H, J=6 Hz), 3.13 (s, 3H), 3.98 (q, 2H, J=7 Hz), 4.2 (t, 2H, J=6.8 Hz), 4.28 (q, 2H, J=7 Hz), 6.87 (dm, 2H, J=9 Hz, unresolved), 6.95 (s, 1H), 7.23 (dm, 2H, J=9 Hz, unresolved), 7.33 (dm, 2H, J=9 Hz, unresolved), 7.73 (dm, 2H, J=9 Hz, unresolved).

25
20
13C-NMR (125 MHz; CDCl₃): δ 14.3, 15.5, 35.0, 37.3, 61.0, 67.5, 68.1, 114.4, 122.0, 123.8, 126.6, 130.5, 131.7, 137.7, 143.1, 147.9, 159.0, 164.9.

d) 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester

25
30
20
15
10
5
2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (1.47 g; 3.38 mmole) was hydrogenated for 3 hours at atmospheric pressure in ethyl acetate (50 ml) using Pd/C (5 %; 0.75 g) as catalyst. The reaction mixture was filtered through celite and dried (magnesium sulfate). The solvent was evaporated *in vacuo* to give

(1.44 g; yield 98 %) of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic acid ethyl ester.

¹H-NMR (500 MHz; CDCl₃): δ 1.16 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.92-2.96 (m, 2H), 3.09 (t, 2H, J=6.6), 3.13 (s, 3H), 3.31-3.38 (m, 1H), 3.56-3.63 (m, 1H), 3.94-3.98 (m, 1H), 4.12-4.19 (m, 4H), 6.8 (dm, 2H, J=8.8 Hz, unresolved), 7.14 (dm, 2H, J=8.9 Hz, unresolved), 7.22 (dm, 2H, J=8.9 Hz, unresolved), 7.33 (dm, 2H, J=8.6 Hz, unresolved).
¹³C-NMR (125 MHz; CDCl₃): δ 14.2, 15.0, 35.1, 37.2, 38.4, 60.7, 66.1, 68.1, 80.3, 114.3, 121.9, 129.5, 130.4, 130.5, 138.0, 147.8, 157.4, 172.5.

10

e) 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

Lithium hydroxide hydrate (0.12 g; 2.82 mmole) dissolved in water (10 ml) was slowly added to a solution of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester (1.12 g; 2.56 mmole) in tetrahydrofuran (30 ml). After stirring at room temperature for 3 hours, water (50 ml) was added and tetrahydrofuran was removed by evaporation *in vacuo*. The water residue was acidified with hydrochloric acid (2M) and extracted three times with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and the solvent was evaporated *in vacuo* to give 1 g (yield 96 %) of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid.

¹H-NMR (500 MHz; CDCl₃): δ 1.17 (t, 3H, J=7 Hz), 2.91-2.99 (m, 1H), 3.03-3.11 (m, 3H), 3.12 (s, 3H), 3.39-3.47 (m, 1H), 3.57-3.64 (m, 1H), 4.01-4.06 (m, 1H), 4.14 (t, 2H, J=6.7 Hz), 6.81 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz, unresolved), 7.22 (dm, 2H, J=8.6 Hz, unresolved), 7.33 (dm, 2H, J=8.6 Hz, unresolved).
¹³C-NMR (125 MHz; CDCl₃): δ 15.0, 35.1, 37.2, 37.8, 66.8, 68.1, 79.7, 114.4, 121.9, 128.8, 130.49, 130.52, 137.9, 147.8, 157.5, 169.1.

f) (S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic amide.

A solution of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid (10.5 g; 25.7 mmole) in dry dichloromethane (150 ml) was cooled on an ice-bath and EDC (5.42 g; 28.3 mmole), diisopropylethylamine (4.8 ml; 28.3 mmole) and HOBt_HO (3.82 g; 28.3 mmole) were added. After 20 minutes the ice-bath was removed and (R)-phenylglycinol (3.88 g; 28.3 mmole) was added. After stirring at room temperature over night dichloromethane (100 ml), citric acid (60 ml, 10 %) and ethyl acetate were added and the phases were separated. The organic phase was washed with citric acid (60 ml), sodium bicarbonate (2 x 60 ml) and brine (60 ml), dried (sodium sulfate), filtered and the solvent evaporated *in vacuo*. The crude product was crystallized twice in ethyl acetate/heptan to give 4.43 g of (R)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide. The mother liquids were combined, the solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel using ethyl acetate:heptan (gradient 25 to 100 % ethyl acetate) to give 5.14 g (yield 38 %) of (S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)-phenyl]propanoic amide and 0.51 g (totally 4.94 g, yield 36 %) of (R)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)-3-[4-(2-{4-methanesulfonyloxyphenyl})-ethoxy)phenyl]propanoic amide.

¹H-NMR (600 MHz; DMSO-d₆): δ 1.04 (t, 3H, J=7.0 Hz), 2.74 (dd, 1H, J=13.9 and 7.6 Hz), 2.84 (dd, 1H, J=13.9 and 5.3 Hz), 3.05 (t, 2H, J=6.7 Hz), 3.30 (m, 1H), 3.34 (s, 3H), 3.44 (m, 1H), 3.55 (t, 2H, J=5.8 Hz), 3.88 (dd, 1H, J=7.3 and 5.5 Hz), 4.15 (t, 2H, J=6.7 Hz), 4.83 (m, 1H), 4.85 (t, 1 OH, J=5.4 Hz), 6.80 (d, 2H, J=8.4 Hz), 7.09 (d, 2H, J=8.4 Hz), 7.17 (m, 3H), 7.23 (m, 2H), 7.28 (d, 2H, J=8.3 Hz), 7.43 (d, 2H, J=8.3 Hz), 8.06 (d, 1 NH, J=8.2 Hz).

¹³C-NMR (150 MHz; DMSO-d₆): δ 15.2, 34.4, 37.5, 38.0, 54.6, 64.5, 65.1, 67.9, 81.1, 114.2, 122.2, 126.8, 127.0, 128.1, 129.8, 130.4, 130.7, 138.1, 141.2, 147.8, 157.0, 171.1.

g) (S)-2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

(S)-2-Ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide (4.49 g; 8.59 mmole), concentrated sulfuric acid (12.5 ml), dioxan (50 ml) and water (50 ml) were stirred at 80° C for 6 hours. After cooling, water (100 ml) was added and the product was extracted with dichloromethane (2 x 100 ml). The organic phases were combined and washed with brine (60 ml), dried (sodium sulfate), filtered and evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate:acetic acid (10:10:1) as gradient and azeotropic destillation with toluen gave 2.78 g (yield 79 %) of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid.

¹H-NMR (600 MHz; DMSO-d₆): δ 1.02 (t, 3H, J=7.0 Hz), 2.78 (dd, 1H, J=13.9 and 8.0 Hz), 2.86 (dd, 1H, J=13.9 and 5.2 Hz), 3.04 (t, 2H, J=6.8 Hz), 3.28 (dq, 1H, J=9.1 and 7.0 Hz), 3.35 (s, 3H), 3.49 (dq, 1H, J=9.1 and 7.0 Hz), 3.92 (dd, 1H, J=5.2 and 7.7 Hz), 4.15 (t, 2H, J=6.8 Hz), 6.82 (d, 2H, J=8.7 Hz), 7.11 (d, 2H, J=8.7 Hz), 7.27 (d, 2H, J=8.5 Hz), 7.42 (d, 2H, J=8.5 Hz), 12.59 (s, br, 1 OH).
¹³C-NMR (150 MHz; DMSO-d₆): δ 15.2, 34.4, 37.5, 37.7, 65.0, 67.9, 79.4, 114.2, 122.2, 129.6, 130.4, 130.7, 138.0, 147.8, 157.1, 173.4.

20

Example 2.

(S)-2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

a) 3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester

25

Tetramethylguanidine (33 g; 0.286 mole) was added to a solution of 4-benzyloxybenzaldehyde (59.1 g; 0.278 mole) and (1,2-diethoxy-2-oxyethyl) (triphenyl) phosphonium chloride (101.8 g; 0.237 mole) in dichloromethane (600 ml) at 0°C. After stirring at room temperature over night, the solvent was evaporated *in vacuo*. The residue was dissolved in diethyl ether, insoluble material was filtered off and the filtrate was

evaporated. The residue was stirred over night with sodium bisulfite (saturated water solution) and diethyl ether. The solid material was filtered off, the filtrate was extracted with diethyl ether, dried (magnesium sulfate) and the solvent was evaporated *in vacuo*. Purification of the crude product by flash chromatography and crystallization in isopropanol gave 66.8 g (yield 86.3 %) of 3-(4-benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester.

¹³C-NMR (125 MHz; CDCl₃): δ 14.4, 15.6, 61.0, 67.5, 70.0, 114.8, 124.0, 126.7, 127.5, 128.1, 128.6, 131.7, 136.7, 143.1, 159.2, 165.0.

10

b) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (0.5 g; 1.5 mmole) was hydrogenated at atmospheric pressure using rhodium on charcoal as catalyst (5%, 50 mg) in methanol (20 ml). The crude product was purified by chromatography using heptane:ethyl acetate (5:1) as eluant to give 50 mg (yield 10%) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester.

¹H NMR (300 MHz; CDCl₃): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8 Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).

¹³C NMR (75 MHz; CDCl₃): δ 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

25

c) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid

Lithium hydroxide hydrate (7.4 g; 177 mmole) dissolved in water (150 ml) was added to a solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester (23.25 g; 70.8 mmole) in dioxan (150 ml). After stirring at room temperature over night dioxan was

evaporated *in vacuo*, water was added and the mixture was washed with diethyl ether. The water phase was acidified with hydrochloric acid (1 M) and extracted with ethyl acetate. The organic phase was washed with water and brine, dried and the solvent was evaporated *in vacuo* to give 21.1 g (yield 99.2 %) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid.

5

¹H NMR (300 MHz; CDCl₃): δ 1.15 (t, 3H), 2.9-3.1 (m, 2H), 3.35-3.45 (m, 1H), 3.6-3.7 (m, 1H), 3.95-3.41 (m, 1H), 5.05 (s, 2H), 6.95 (d, 2H), 7.2 (d, 2H), 7.25-7.5 (m, 5H).
¹³C NMR (75 MHz; CDCl₃): δ 15.0, 38.1, 66.6, 70.0, 79.9, 114.7, 127.5, 128.0, 128.6, 129.3, 130.5, 137.1, 157.7, 176.3.

10

d) 3-(4-Benzylxyphenyl)-(S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)propanoic amide

A solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid (2.92 g, 9.74 mmole) in dry dichloromethane (30 ml) was cooled on an ice-bath and EDC (2.03 g; 10.61 mmole),
15 diisopropylethylamine (1.84 ml, 10.61 mmole) and HOBr x H₂O (1.43 g; 10.61 mmole) were added. After 30 minutes the ice-bath was removed and (R)-phenylglycinol (1.46 g, 10.61 mmole) was added. After stirring at room temperature over night ethyl acetate (100 ml) was added and the mixture was washed with potassium hydrogensulfate (1 M), saturated sodium bicarbonate solution, sodium carbonate solution and brine. The organic
20 phase was dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using ethyl acetate:heptan to give 1.5 g (yield 37 %) of 3-(4-benzyloxyphenyl)-(S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)propanoic amide and 1.25 g (yield 31 %) of 3-(4-benzyloxyphenyl)-(R)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)propanoic amide.

25

¹H NMR (400 MHz; CDCl₃): δ 7.43-7.27 (m, 8H), 7.22 (d, J=8.3 Hz, 4H), 7.13 (d, NH, J=7.8 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 5.08 (s, 2H), 5.01 (m, 1H), 3.99 (dd, J=6.8 and 3.9 Hz, 1H), 3.69 (m, 2H), 3.50 (q, J=6.8 Hz, 2H), 3.15 (dd, J=14.2 and 3.9 Hz, 1H), 2.97 (dd, J=14.2 and 6.8 Hz, 1H), 2.94 (m, OH, 1H),
30 1.16 (t, J=6.8 Hz, 3H).

¹³C NMR (100 MHz; CDCl₃): δ 172.3, 157.5, 138.9, 137.0, 130.7, 129.4, 128.6, 128.4, 127.7, 127.6, 127.3, 126.5, 114.4, 81.0, 69.8, 66.3, 66.0, 55.3, 37.8, 15.1.

5 e) 3-(4-Benzylxyphenyl)-(S)-2-ethoxypropanoic acid

3-(4-Benzylxyphenyl)-(S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)propanoic amide (8.9 g; 21.22 mmole) was hydrolyzed with concentrated sulfuric acid (27 ml) in water (104 ml) and dioxane (104 ml) at 90° C for 5 hours. The reaction mixture was poured onto water 10 (220 ml) and extracted with ethyl acetate. The organic phase was washed with brine, dried (sodium sulfate) and the solvent was evaporated *in vacuo* to give 6.85 g of a mixture of 3-(4-benzylxyphenyl)-2-(S)-ethoxypropanoic acid and (S)-2-ethoxy-3-(4-hydroxyphenyl)-propanoic acid, which was used without further purification.

15 ¹H NMR (400 MHz; CDCl₃): δ 7.47-7.30 (m, 5H), 7.19 (d, J=8.8, 2H), 6.93 (d, J=8.8 Hz, 2H), 5.10 (s, 2H), 4.06 (dd, J=7.8 and 4.4 Hz, 1H), 3.64 (dq, J=9.8 and 6.8 Hz, 1H), 3.44 (dq, J=9.8 and 6.8 Hz, 1H), 3.09 (dd, J=14.2 and 4.4 Hz, 1H), 2.98 (dd, J=14.2 and 7.8 Hz, 1H), 1.19 (t, J=6.8 Hz, 3H).

20 f) 3-(4-Benzylxyphenyl)-(S)-2-ethoxypropanoic acid ethyl ester

Hydrogen chloride (g) was bubbled through a solution of 3-(4-benzylxyphenyl)-2-(S)-ethoxypropanoic acid (6.85 g) in ethanol (400 ml). Thionyl chloride (2 ml, 27.4 mmole) was slowly added and the reaction mixture was refluxed for 2 hours. The solvent was 25 evaporated *in vacuo* to give 8 g of a mixture of 3-(4-benzylxyphenyl)-(S)-2-ethoxypropanoic acid ethyl ester and (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester which was used without further purification.

30 ¹H NMR (300 MHz; CDCl₃): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8

Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).

¹³C NMR (75 MHz; CDCl₃): δ 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

5

g) (S)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)- (S)-2-ethoxypropanoic acid ethyl ester was hydrogenated at atmospheric pressure for 2 hours in ethyl acetate using Pd/C as catalyst. Purification by chromatography on silica gel using toluen:ethyl acetate as eluant gave 3.83 g (yield in 3 steps 76 %) of (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

¹H-NMR (400 MHz; CDCl₃): δ 1.18 (t, 3H, J=6.8 Hz), 1.24 (t, 3H, J=7 Hz), 2.96 (d, 2H, J=6.5 Hz), 3.34-3.43 (m, 1H), 3.57-3.66 (m, 1H), 4.00 (t, 1H, 6.5 Hz), 4.18 (q, 2H, J=7 Hz), 5.30 (s, 1 OH), 6.74 (dm, 2H, J=8.5 Hz, unresolved), 7.10 (dm, 2H, J=8.5 Hz, unresolved).

¹³C-NMR (100 MHz; CDCl₃): δ 14.2, 15.0, 38.4, 60.9, 66.2, 80.4, 115.1, 129.0, 130.5, 154.5, 172.7.

20 h) (S)-2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester

A solution of 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate (described in Example 1a) (2.41 g; 8.14 mmole) in acetonitrile (11.8 ml) was added to a mixture of (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (1.3 g; 5.46 mmole), potassium carbonate (2.26 g; 16.4 mmole) and magnesium sulfate (1 g) in acetonitrile (50 ml). The reaction mixture was refluxed for 19 hours. More of 2-(4-methanesulfonyloxyphenyl)ethyl-methanesulfonate (0.8 g; 2.73 mmole) was added and the reaction mixture was refluxed for another 25 hours. Solid material was filtered off and the

solvent was evaporated *in vacuo* to give 3.6 g of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester.

i) (S)-2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

Lithium hydroxide hydrate (0.229 g; 5.45 mmole) dissolved in water (6 ml) was slowly added to a mixture of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester (2.29 g; 5.24 mmole) in tetrahydrofuran (50 ml) and water (10 ml) at 5° C. The reaction mixture was stirred at 5° C for 2.5 hours, at 20° C for 3 hours, at 10° C for 15 hours and at 20° C for 3.5 hours. More lithium hydroxide hydrate (44 mg, 1.05 mmole) dissolved in water (1 ml) was added at 10° C. After another 21.5 hours of stirring at 10° C, more lithium hydroxide hydrate (44 mg; 1.05 mmole) dissolved in water (1 ml) was added. The reaction mixture was stirred at 25° C for 3 hours and then kept at 2° C for 15 hours. Tetrahydrofuran was evaporated *in vacuo* and then water and ethyl acetate were added. Insoluble material was filtered off and the phases of the filtrate were separated. The water phase was washed twice with ethyl acetate, acidified with hydrochloric acid (2 M; 3.2 ml) and extracted with ethyl acetate (30 ml). The organic phase was washed twice with water, dried (magnesium sulfate), filtered and the solvent was evaporated *in vacuo* to give 1.9 g (yield 72 % in 2 steps) of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid.

¹H-NMR (600 MHz; DMSO-d₆): δ 1.02 (t, 3H, J=7.0 Hz), 2.78 (dd, 1H, J=13.9 and 8.0 Hz), 2.86 (dd, 1H, J=13.9 and 5.2 Hz), 3.04 (t, 2H, J=6.8 Hz), 3.28 (dq, 1H, J=9.1 and 7.0 Hz), 3.35 (s, 3H), 3.49 (dq, 1H, J=9.1 and 7.0 Hz), 3.92 (dd, 1H, J=5.2 and 7.7 Hz), 4.15 (t, 2H, J=6.8 Hz), 6.82 (d, 2H, J=8.7 Hz), 7.11 (d, 2H, J=8.7 Hz), 7.27 (d, 2H, J=8 .5 Hz), 7.42 (d, 2H, J=8.5 Hz), 12.59 (s, br, 1 OH).

¹³C-NMR (150 MHz; DMSO-d₆): δ 15.2, 34.4, 37.5, 37.7, 65.0, 67.9, 79.4, 114.2, 122.2, 129.6, 130.4, 130.7, 138.0, 147.8, 157.1, 173.4.

Biological activity

The biological activity of the compound of the invention was tested in obese diabetic mice of the Umeå ob/ob strain. Groups of mice received the test compound by gavage once 5 daily for 7 days. On the last day of the experiment the animals were anesthetized 2h after dose in a non-fed state and blood was collected from an incised artery. Plasma was analyzed for concentration of glucose, insulin and triglycerides. A group of untreated obese diabetic mice of the same age served as control. The weight of the mice was measured before and after the experiment and the obtained weight gain was compared to the weight 10 gain of the control animals. The individual values for glucose, insulin and triglyceride levels of the mice from the test group were expressed as the percent rage of the corresponding values from the control group.

The desired "therapeutic effect" was calculated as the average percent reduction of the three variables glucose, insulin and triglycerides below the levels in the control animals. 15 The therapeutic effect of the tested compounds according to the invention was compared to the same effect in the prior art compound troglitazone, administrered by gavage in the oral dose of 100 µmol/kg for 7 days.

20 The superior effects of the tested compound according to the invention compared to that of troglitazone when given in the same oral dose demonstrate the increased potency and efficiency of the claimed compound.

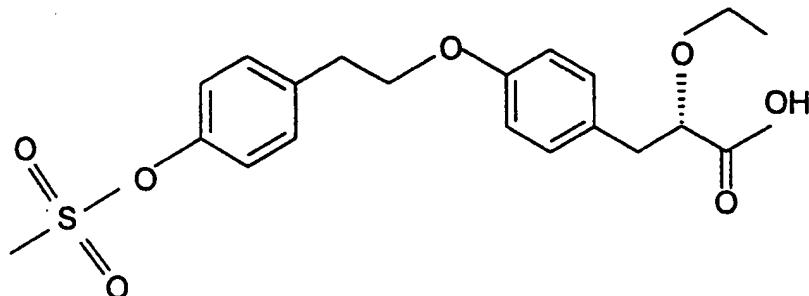
Abbreviations

- 25 NIDDM non insulin dependent diabetes mellitus
VLDL very low density lipoproteins
HDL high density lipoproteins
IRS insulin resistance syndrom
PPAR peroxisome proliferator activated receptor
30 DEAD diethyl azodicarboxylate

	ADDP	azodicarbonyl dipiperidine
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	EDCxHCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	DCC	dicyclohexylcarbodiimide
5	HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	TBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
	PyBop	benzotriazole-1-yl-oxy-tris-pyrolidino-phosphonium hexafluorophosphate
	DMF	dimethylformamide
	DMAP	4-dimethylaminopyridine
10	TEA	triethylamine
	DiPEA	diisopropylethylamine
	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	COD	cyclooctadiene
	LDA	lithium diisopropylamide
15	LHMDS	lithium hexamethyldisilylamine
	TLC	thin layer chromatography
	THF	tetrahydrofuran
	Pd/C	palladium on charcoal
	HOEt x H ₂ O	1-hydroxybenzotriazole-hydrate
20	m	multiplet
	t	triplet
	s	singlet
	d	doublet
	q	quartet
25	qvint	quintet
	br	broad
	dm	multiplet of doublet
	rac	racemate

CLAIMS

1. A compound having the formula

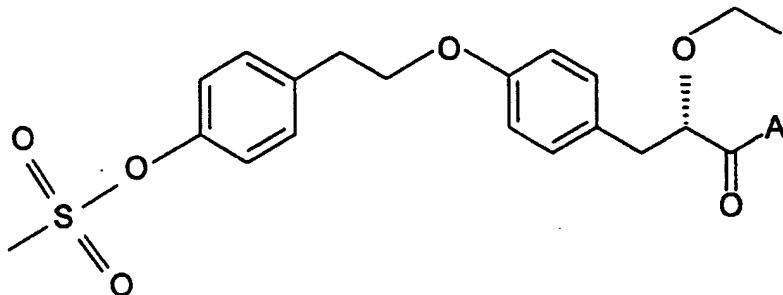


5

and pharmaceutically acceptable salts, solvates, and crystalline forms thereof.

10 2. A process for the preparation of a compound according to claim 1, characterized by

a) converting a compound of the formula II

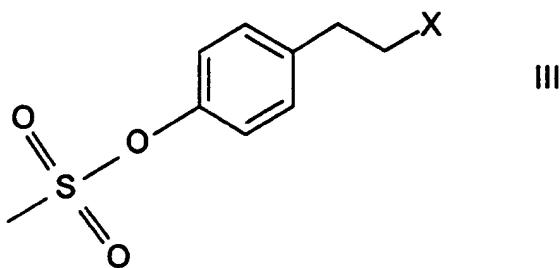


15

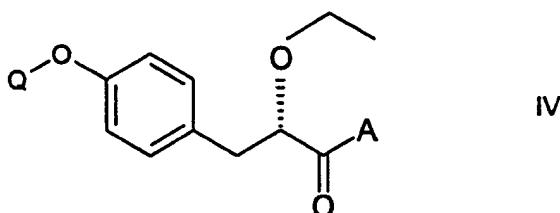
wherein A is a chiral auxiliary group or the group -OR^P, wherein R^P is a protective group,
or

b) reacting a compound of the formula III

20



with a compound of the formula IV

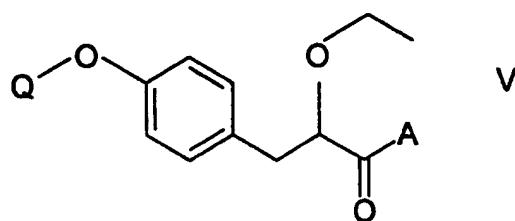


5

in which formulas A is -OH, a chiral auxiliary group or the group -OR^P, wherein R^P is a protective group, X is -OH or a leaving group and Q is H, whereafter, if necessary, hydrolysing the obtained compound, or

10

c) diastereoisomerically separating a compound of the formula V

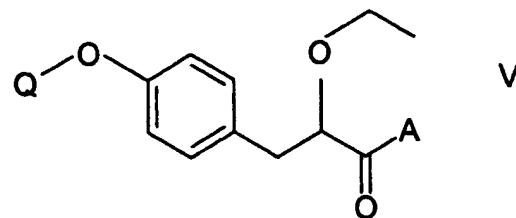


15

wherein Q is -CH₂CH₂Ph-4-OSO₂CH₃ and A is a chiral auxiliary group, whereafter hydrolysing the obtained compound, or

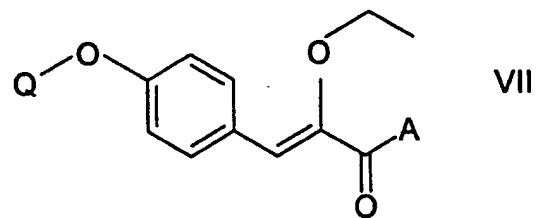
d) enantiomerically separating a compound of the formula V

20



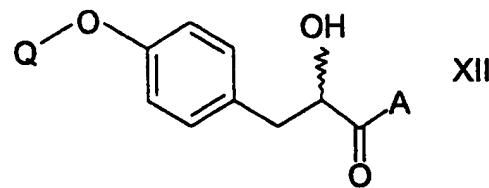
wherein Q is $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$ and A is $-\text{OH}$ or $-\text{OR}^{\text{P}}$, wherein R^{P} is a protective group, whereafter, if necessary hydrolysing the obtained compound, or

e) asymmetrically reducing a compound of the formula VII



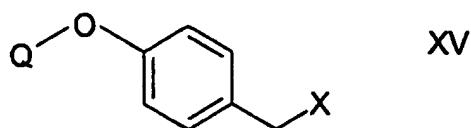
wherein Q is $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$ and A is $-\text{OH}$, a chiral auxiliary group or the group $-\text{OR}^{\text{P}}$, wherein R^{P} is a protective group, whereafter, if necessary, hydrolysing the obtained compound, or

f) alkylating a compound of the formula XII

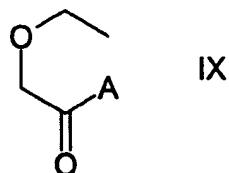


wherein Q is $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$ and A is $-\text{OH}$, a chiral auxiliary group or the group $-\text{QR}^{\text{P}}$, wherein R^{P} is a protective group, whereafter, if necessary, hydrolysing the obtained compound, or

g) reacting a compound of the formula XV



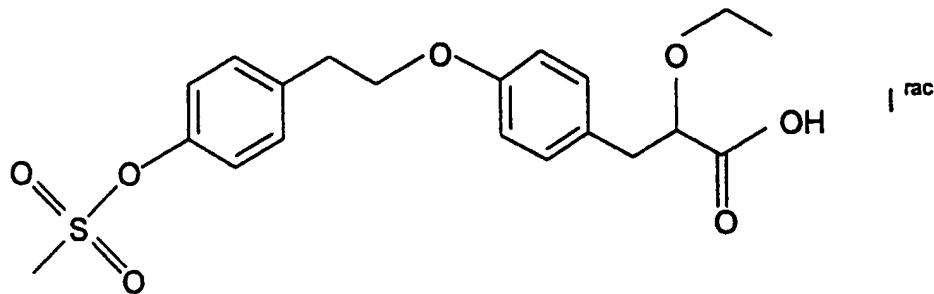
5 with a compound of the formula IX



in which formulas X is a leaving group, Q is $-\text{CH}_2\text{CH}_2\text{Ph}-4-\text{OSO}_2\text{CH}_3$ and A is a chiral
auxiliary group used to induce chirality in the product whereafter, hydrolysing the obtained
compound, or

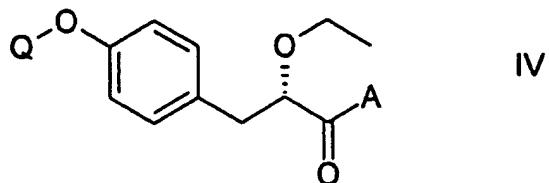
h) resolving a racemate of the formula I^{rac}

15



whereafter, if desired, the compound obtained according to any of methods a)-h) is converted to a pharmaceutically acceptable salt, and/or a solvate such as a hydrate thereof.

20 3. A compound of the formula IV



wherein Q is hydrogen and A is -OH, a chiral auxiliary group or the group -OR^P, wherein R^P is a protective group.

5

4. A compound according to claim 3, wherein in formula IV A is -OH or alkoxy having 1 to 3 carbon atoms.

10

5. A compound according to claim 1 for use in therapy.

6. A pharmaceutical formulation containing a compound according to claim 1 as active ingredient optionally together with a pharmaceutically acceptable carrier, adjuvant and/or diluent.

15 7. The use of a compound according to claim 1 in the manufacture of a medicament for the prophylaxis and/or treatment of clinical conditions associated with insulin resistance.

8. A method for the prophylaxis and/or treatment of clinical conditions associated with insulin resistance wherein a therapeutically active amount of a compound according to claim 1 is administered to a mammal in the need of such prophylaxis and/or treatment.

20 9. A method according to claim 8 wherein the prophylaxis and/or treatment of clinical conditions associated with insulin resistance is the prophylaxis and/or treatment of dyslipidaemia in such conditions.

25

10. A method according to claim 8 wherein the prophylaxis and/or treatment of clinical conditions associated with insulin resistance is the prophylaxis and/or treatment of hyperglycaemia in non insulin dependent diabetes mellitus.
- 5 11. A pharmaceutical formulation for use in the prophylaxis and/or treatment of clinical conditions associated with insulin resistance wherein the active ingredient is a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00941

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 309/66, A61K 31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1997:684384, document no. 127:307307, Sankyo Co., Ltd., et al: "Preparation of phenylalkylcarboxylic acid derivatives lowering blood sugar level"; WO,A1,9737970, 19971016 --	3,4
X	Tetrahedron Letters, Volume 35, No 19, 1994, Geoffrey G. Cox et al, "Competing O-H Insertion and Beta-Elimination in Rhodium Carbenoid Reactions; Synthesis of 2-Alkoxy-3-arylpropanoates" page 3139 - page 3142 --	3-4

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

3 Sept 1999

07-09-1999

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Gerd Strandell/EÖ
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00941

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9731907 A1 (GLAXO GROUP LIMITED), 4 Sept 1997 (04.09.97), page 23, line 25 - page 27, line 4, the claims -- -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00941

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 8-10
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00941

Claims 8-10 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.

PCT/SE 99/00941

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9731907 A1	04/09/97	AP 9700935 D	00/00/00
		AU 2093597 A	16/09/97
		CA 2247443 A	04/09/97
		CZ 9802750 A	13/01/99
		EP 0888317 A	07/01/99
		GB 9604242 D	00/00/00
		HR 970110 A	30/04/98
		NO 983940 A	27/10/98
		PL 328871 A	01/03/99

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.